PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2005/001071	22.03.2005	26.03.2004

International Patent Classification (IPC) or both national classification and IPC
C07D231/38, C07D403/04, C07D409/04, C07D405/12, C07D403/12, C07D403/10, A61K31/415, A61P31/12

Applicant
GLAXO GROUP LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2005/001071

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2005/001071

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 3-5

because:

☒ the said international application, or the said claims Nos. 3-5 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2005/001071

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-13
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-13
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1, 2, 6-13
	No:	Claims	

2. Citations and explanations

see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/GB2005/001071

III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 3-5 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

V Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.1 The present invention relates to 4-carboxy pyrazole derivatives useful as anti-viral agents.

V.2 Reference is made to the following documents:

D1: WO 03/037895 A
D2: WO 03/037893 A
D3: WO 2004/076415 A (GLAXO GROUP LIMITED; BRAVI, GIANPAOLO; BURTON, GEORGE; HOWES, PETER DA) 10 September 2004 (2004-09-10)
D4: WO 2004/096210 A (GLAXO GROUP LIMITED; BRAVI, GIANPAOLO; GRIMES, RICHARD, MARTIN; GUIDET) 11 November 2004 (2004-11-11)

Documents D3 and D4 were published after the priority date. In the presumption the priority is valid these documents are not regarded as prior art.

V.3 Novelty

Document D1 discloses heteroacyl pyrrolidine derivatives as HCV inhibitors.
Document D2 discloses acyl dihydro pyrrole derivatives as HCV inhibitors.
It is noted that document D3 discloses 1-(hetero)aroyl)-pyrrolidine-2-carboxylic acid derivatives useful as anti viral agents.
It is noted that document D4 discloses acylated indoline and tetrahydroquinoline derivatives as HCV inhibitors.

A compound of formula I is disclosed in none of the documents. Claims 1 and 2 therefore fulfill the requirements of Art 33(2) PCT.

Claims 3-5 describe a method of treatment comprising administering a compound of formula I and are novel by consequence.

Claims 6-8 describe a compound of formula I for use in medical therapy and are novel by consequence.

Claim 9 describes a pharmaceutical formulation comprising a compound of formula I and is novel by consequence.

Claims 10 and 11 describe a process for the preparation of a compound of formula I and are novel by consequence.

Claims 12 and 13 describe the use of a compound of formula I in the manufacture of a medicament and are novel by consequence.

V.4 Inventive step

Starting from documents D1 and D2 the problem to be solved by the present application may be regarded as how to provide novel possibly improved compounds which can act as inhibitors of HCV. The applicant shows on page 123 lines 1-7 that certain compounds have an IC_{50} of <80µM when tested in an assay to inhibit NS5B wildtype HCV polymerase. As the compounds of the present application have not been made obvious by the prior art, the solution of the applicant may be regarded to involve an inventive step (Art 33(3) PCT).

V.5 Industrial applicability

For the assessment of the present claims 3-5 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to

the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

VI Certain documents cited

WO 2004/076415 A
WO 2004/096210 A